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The goal of this study is to evaluate the differences in readability and content between U.S. drug Package Inserts (PI) and Consumer Medical Information Leaflets (CMI). Using text mining techniques such as Natural Language Processing with the UMLS MetaMap, and document metrics such as the Flesch-Kincaid grade level score, a sample of PI and CMI will be examined for 35 common drugs in the U.S.

Text Mining allows for mapping of text into Concept Unique Identifiers, which allows for comparison of text between documents with different vocabularies. As Package Inserts are written for professionals, and CMI Leaflets are written for consumers, this technique lends itself well to compare content.

This study shows that recall is appropriately low when comparing CMI Leaflets to Package Inserts: omitted concepts are more important for physicians and pharmacists than patients. Readability is high for CMI Leaflets, but more effort should be made to express contraindications.

Headings:

Text Mining

Health Informatics

Prescription Drugs

AN ANALYSIS OF PRESCRIPTION DRUG INFORMATION FROM MANUFACTURER TO CONSUMER: A TEXT MINING APPROACH

by
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of the School of Information and Library Science
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INTRODUCTION

A patient waits in his local pharmacy for his prescription to be filled. While he waits, the pharmacist performs a series of steps to get the patient his medication. The pharmacist verifies that the drug dosage is appropriate, checks the patient's record in the pharmacy database to make sure there are no obvious reasons the patient should not be given the drug, such as allergies, and measures the amount to be dispensed. The pharmacist then applies information to the bottle, applying directions and warnings via an array of stickers, and then hands it to the pharmacy technician. The technician prints a leaflet with more information about the prescription for the patient, staples it to the bag, and asks the patient if he has any questions about the prescribed drug while he pays for it. The patient likely assumes he has been told all pertinent information he requires to take the medication properly, and can reference the leaflet at a later time if necessary.

The routine is virtually the same for millions of Americans: a patient visits his doctor, who examines and tests him, and produces a diagnosis. When a drug is appropriate to treat the condition, the doctor will write a prescription. He chooses the course of therapy to be prescribed based on the drugs available for the patient's condition, as well as the patient's medical history, including any allergies.

In this study, Consumer Medical Information (CMI) Leaflets will be evaluated for completeness and readability and compared to Package Inserts (PI) as the gold standard. CMI contains a summary of precautions and instructions for the drugs a patient has been prescribed, and is information often printed at the pharmacy counter. The CMI is information generally bought by the pharmacy from an outside company, which bases

the summary on the PI. The PI is an FDA-approved document written for health professionals by the drug manufacturer that contains detailed information about the drug produced and is included in the packaging.

To accomplish the comparison of these two documents, the experiment will use Computational Linguistics techniques such as text mining and Natural Language Processing (NLP). MetaMap, a Unified Medical Language System (UMLS) tool hosted by the National Library of Medicine will be used for NLP, and the Flesch-Kincaid grade level score will be used to measure readability.

The following research questions will be addressed:

1. How does the information in the Package Insert differ from the information in the CMI Leaflet?
2. How do Package Inserts and CMI Leaflets compare in readability?

LITERATURE REVIEW

The flow of drug information to the consumer is complex. Sources of information directly provided to consumers include: doctors, pharmacists, Package Inserts, and CMI Leaflets. A combination of any of these resources may be used by consumers, and these information sources all transfer information differently.

Package Inserts are the *de facto* standard of publicly available, FDA-approved written information about prescription drugs. However, they are sufficiently difficult to read to be considered significantly above the threshold of comprehensibility of the average consumer. They contain all information required by professionals who prescribe and advise patients about how they may use the drug. By law, they are distributed by the pharmaceutical manufacturer with every prescription drug they produce that is sold in the United States (FDA, June 2009).

In response to the consumer's need for drug information to accompany their prescriptions, as well as increasing requirement for patient counseling, many pharmacies began to distribute CMI Leaflets with prescriptions in the early 1990's. CMI Leaflets are designed to be an easily read resource which relays how to safely use prescribed medications. These leaflets are not required by law, but are widely distributed as a self-regulatory effort, following FDA recommendations. Information in the leaflets is generally based on the FDA-approved Package Insert and the leaflets are distributed by a variety of information publishers. However, as their content is not regulated by the FDA, the format, quality, and usability of these documents varies.

The Physician's Desktop Reference (PDR) is a compendium that is used as a primary source of drug information for physicians. It is published by a private-sector publisher, Thomson Medical Economics, and was originally conceived as a promotional publication for drugs. Pharmaceutical companies are not legally required to submit information about their drugs to the publisher of the PDR, but do so willingly as a basic type of drug marketing process. As the PDR is a commercial product, drug companies must pay to be included in the publication. The publisher also states that the drug manufacturers are solely responsible for the accuracy of the information submitted for publication (Thornton, 2003). As there is little regulatory control over this compendium, there is some potential cause for concern as to the accuracy of the information published (Cohen, 2001).

Information flow for patients generally originates from the prescribing physician, who typically advises the patient of the new prescription, and provides varying degrees of details about the medication to the patient. When a patient has a prescription filled at a pharmacy, the patient may ask to consult with the pharmacist. The pharmacist may have additional information including possible drug interactions or special precautions, and the patient is given written information such as the CMI Leaflet, and possibly the Package

Insert. Figure 1 summarizes these information flows.

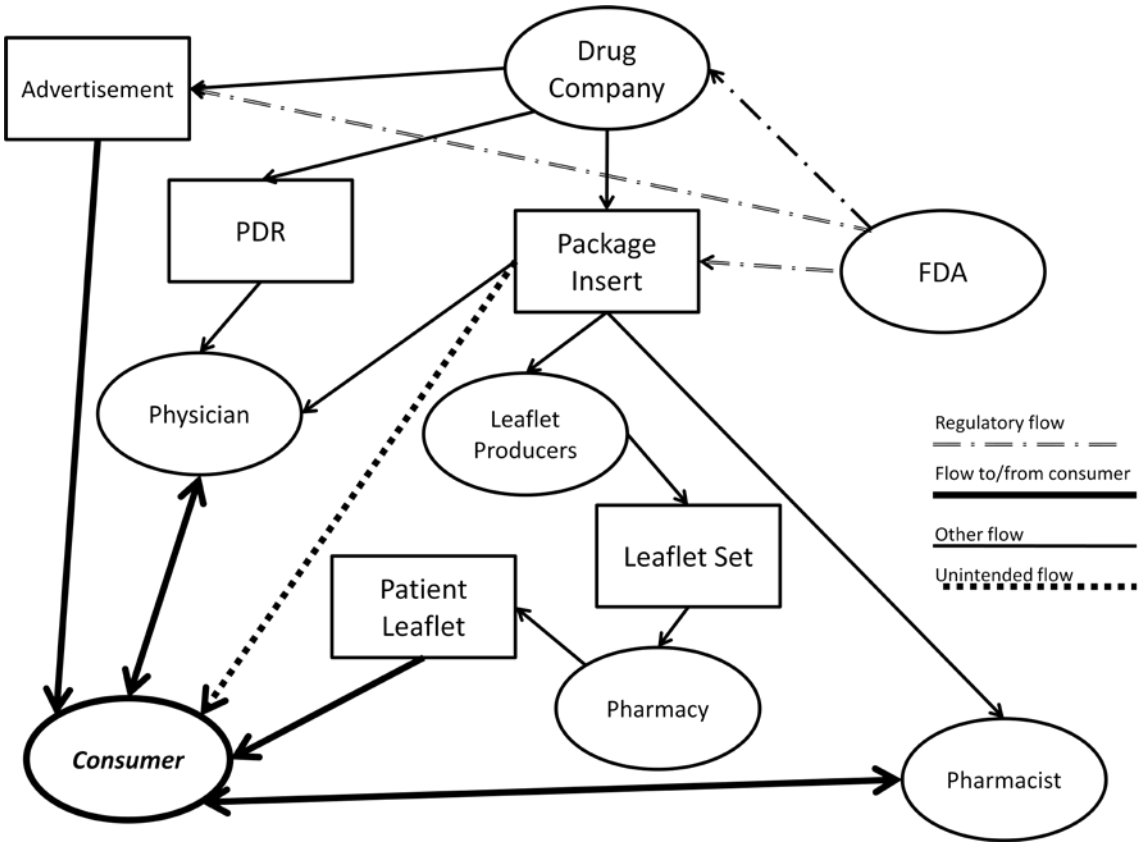


Figure 1: Possible flows of drug information to consumers

An assumption in this information flow is that physicians know the patient's histories, allergies, and other mitigating factors in prescribing a therapy and the pharmacist will have records of other prescriptions, to help prevent drug-drug interactions, if applicable. However, this assumption is over-simplified.

Given that patients in the U.S. generally do not exclusively see one doctor, each individual physician that sees the patient may not have a complete patient history and full knowledge of a patient's co-occurring therapies. Patients may also have prescriptions filled at several pharmacies. Some health insurance policies require patients to fill some

prescriptions, particularly long-term medications, through a pharmacy of the company's choice, rather than the patient's.

Additionally, many long-term prescriptions are filled using mail order pharmacies which potentially have no pharmacist-patient interaction, relying completely on written counseling. Because medications are being dispensed by multiple pharmacies, pharmacists may not be aware of dangers, such as potential drug interactions, which the patient may be exposed to.

Patients who see multiple doctors or pharmacists cannot assume that all relevant information is being given to them for every drug they are prescribed, as their physicians and pharmacists may not have complete information of the patient. Therefore, patients must play an active role in acquiring drug information for themselves.

Initially, the FDA required "Patient Package Inserts" (PPI), consumer-readable information about the drug included with the Package Inserts (PI) for selected drugs in 1968. Research had shown a correlation between extensive use of the drug isoproterenol and the condition bronchoconstriction, which prompted the FDA to mandate a brief warning be affixed to its container. In 1970, the FDA required that a PPI accompany oral contraceptives when research showed an association between use of oral contraceptives and various circulatory disorders. Since oral contraceptives, once prescribed, were administered without significant medical supervision, the FDA concluded that patients needed a PPI that directed them to obtain a more detailed information pamphlet from their physician. This information was to supplement professional advice, but not replace it (Schuman, 2002).

The AMA was particularly opposed to the PPI program. At the time, many physicians supported a theory that the potential for suggestibility was heightened by presenting patients with information about a drug's potential side-effects. If the PPI included with medication states that the drug may cause headaches, for example, it might cause patients to have psychogenic headaches simply because the PPI says it is possible for the patient to have that symptom due to the use of the drug (Keyown, Slovic, Lichenstein 1984). Studies conducted at the time of this debate about public availability of drug information, such as the Keown, Slovic and Lichtenstien study, showed that psychogenic or "suggested" side-effects were uncommon. However, while patients were not shown to imagine suggested symptoms, patients were more likely to attribute symptoms, possibly unrelated to their medication, as a side-effect of the medication (Morris, 1981).

Another reason for opposition to mandatory regulated PPI's was the concern that pharmacists would be intruding unnecessarily into the patient/physician relationship and diminish the physician's role in the drug prescription process. The stance of the FDA was that the PPI program was not intended to replace the physician, rather it was intended to supplement individual instruction.

The FDA began a 3-year pilot program to extend the PPI requirement for all drugs in 1979. At the end of the program in 1982, the FDA opted to withdraw its governance of PPI in favor of private-sector self-regulated control of drug information for consumers (Svarstad, Mount, Tabak, 2005). This action was endorsed by such organizations as the American Medical Association (AMA), the American Association of Retired Persons

(AARP), National Council on Patient Information and Education (NCPIE), and the Committee on Patient Education, a FDA entity (Schluster, 1995).

As computer technology advanced in the early 1990's, pharmacies began printing leaflets for patients with new prescriptions, now referred to as Consumer Medicine Information (CMI). These were intended to address increasing state and federal requirements for patient counseling at pharmacies. However, the quality of these earlier leaflets were largely deemed deficient by the FDA due to poor quality of provided information, patient non-adherence, poor patient knowledge and preventable adverse reactions (Svarstad, Mount, Tabak, 2005). Counseling requirements evolved on the state and federal levels because of the perceived complexity of the Package Inserts, which mainly focused on informing professionals, rather than consumers, about the products.

Due to the increase in counseling requirements, there was a subsequent increase in written information, and the fact that the quality of the written information was largely unregulated was questioned by DHHS. Congress requested DHHS develop an action plan to evaluate the extent of this potential problem and authorized the FDA to create an action plan to address deficiencies. The evaluation plan was developed in August, 1996 and was steered by a committee of professionals and consumers from 34 different organizations. The resulting plan became known as the Keystone Criteria (Svarstad, Mount, Tabak, 2005).

Criterion	The information must:
1	Include drug names and indications for use
2	Include contraindications and what to do if applicable
3	Include specific directions about how to use, monitor, and get the most benefit
4	Include specific precautions and how to avoid harm while using it
5	Include symptoms of serious or frequent adverse reactions and what to do
6	Include general information and encouragement to ask questions
7	Be scientifically accurate, unbiased, and up-to-date
8	Be readily comprehensible and legible

Table 1: Keystone Criteria for Consumer Medical Information (Kimberlin, Winterstein, 2008)

Several studies have been done, not just in the U.S., but also internationally, regarding the quality of prescription information provided to consumers. While consumers had access to the professional package insert and were often given CMI leaflets from pharmacies, patients still were not getting the necessary drug information about their prescriptions well into the 2000's.

The need for supplemental instruction for patients was illustrated in a study by Lapointe, Pappas, Deverka, et al. (2006). Consumers were surveyed about information

they had received with Isotretinoin and Estrogen prescriptions. They found that 86% of patients received the FDA-Approved Package Insert, and 75% of the 300 participants felt confident they knew all the information necessary to take their prescribed medication. However, when tested about their knowledge of their prescribed drug, they were unaware of many of the risks of their medication.

Participants were given a questionnaire in which they were to answer "yes" or "no" to five side effects or risks associated with their medication. Their results showed that the mean number of correct responses scored only slightly higher than the threshold achieved from guessing. Fewer than half of the participants knew about the most severe side effects, myocardial infarction and cancer, despite having read the Package Insert or the FDA Medication Guide.

A 2007 study compared the leaflets given to patients in pharmacies in the U.S., the U.K., and Australia (Raynor, Svarstad, Knapp, et al., 2007). A set of four drug leaflets from each area was selected, for four drugs: atenolol, atorvastatin, glyburide, and nitroglycerine. The rating process was conducted manually by two health services researchers and three pharmacist health service researchers. Using the U.S. Keystone guidelines, each drug's leaflet was evaluated by each evaluator for Keystone Criterion 1-6. Since Keystone Criteria 7 and 8 are somewhat subjective, all documents were assessed on these two criteria by one reviewer, and moderated by another reviewer.

It was found that even with the new U.S. Keystone guidelines for information in leaflets, U.S. CMI Leaflets were still deficient in the information they provided. The most frequently omitted information was regarding drug interactions, but they also were

lacking in listing specific precautions. However, the U.S. was not alone, as Patient Leaflets in the U.K. rated similarly as a whole. (Raynor, Svarstad, Knapp, et al., 2007).

A study was also done that directly used the Keystone Criteria to evaluate CMI Leaflets (Svarstad, Mount, Tabak, 2005). Experimenters obtained CMI Leaflets from a variety of pharmacies and in a variety of geographical areas for a fixed list of prescription drugs. The experiment was designed this way in order to obtain the best random sample from all different types of pharmacies, from small independent drug stores to large chain stores. Each leaflet was evaluated manually by experts for congruence between the leaflet and the FDA-approved Package Insert, and also evaluated by consumers for readability. Though the consumer evaluators were satisfied overall with the information, the expert evaluators rated most leaflets as deficient in all Keystone Criteria, with complete agreement that no leaflets reached the "high quality" mark of 80% or higher compliance with the Criterion.

Though several studies have been done to evaluate consumer prescription drug leaflets, they have all used expert evaluators using manual methods of evaluation based on their own experience. In review of pertinent literature, there were no references to attempts at evaluating these criteria automatically. The criterion for evaluation of consumer prescription drug information is well-formed, well-defined, and ready for an automated tool to rate to these criterion as humans would.

In a recent study by Bashyam and Taira (2009), MetaMap (http://mmtx.nlm.nih.gov), a Natural Language Processing (NLP) tool was used to code clinical concepts in clinical reports. To do this, the word elements in the documents were mapped to UMLS Concept Unique Identifiers (CUI) as a step to normalize word tokens

for comparison. The Concept Unique Identifier is a label for unique concepts in the UMLS. Each concept is associated with a semantic type, as well as a definition and any synonyms (see Table 2). The advantage of using this approach is that the problem of different word ordering and synonymy of concepts is solved by eliminating the complexities of language, and storing the contents as a bag-of-concepts instead. Using this method, the authors were able to accurately compare two documents at the conceptual level, rather than at the syntactic and lexical levels.

Term Name	Hypertensive disease
CUI	C0020538
Definition	Persistently high systemic arterial BLOOD PRESSURE. Based on multiple readings (BLOOD PRESSURE DETERMINATION), hypertension is currently defined as when SYSTOLIC PRESSURE is consistently greater than 140 mm Hg or when DIASTOLIC PRESSURE is consistently 90 mm Hg or more. (MSH) persistantly high arterial blood pressure. (CSP) Abnormally high blood pressure. (NCI) Pathological increase in blood pressure; a repeatedly elevated blood pressure exceeding 140 over 90 mmHg. (NCI)
Synonyms	Vascular Hypertensive Disorder vascular hypertension systemic hypertension Systemic arterial hypertension Raised blood pressure (disorder) Pressure, high blood Increased blood pressure Hypertensive vascular disease Hypertensive vascular degeneration Hypertensive disorder, systemic arterial (disorder) Hypertensive disorder HYPERTENSIVE DISEASES Hypertensive disease, NOS Hypertensive disease NOS (disorder) Hypertensive disease NOS Hypertensive disease Hypertensive cardiovascular disease or syndrome Hypertension, NOS Hypertension, arterial Hypertension NOS HYPERTENSION ARTERIAL

	Hypertension Hyperpiesis Hyperpiesia HTN - Hypertension htn HT - Hypertension HT high; blood pressure high; arterial tension high bp High Blood Pressures High blood pressure disorder High blood pressure (& [essential hypertension]) High Blood Pressure HBP - High blood pressure HBP BP+ - Hypertension BP - High blood pressure Blood Pressures, High blood pressure; high Blood Pressure, Increased Blood Pressure, High BLOOD PRESSURE HIGH 3-02 HYPERTENSIVE DISEASES (Hypertensive disease) or (hypertension)

Table 2: Data associated with the CUI representing "Hypertension"

The main benefit to automated evaluation is that it is potentially much less expensive, faster, and can evaluate a larger corpus. This experiment will attempt to use novel text mining techniques as an automated process to evaluate consumer prescription drug information using the Keystone Criteria as a guide.

METHODOLOGY

The goal of the experiment is to use an automated text mining approach to compare the content and readability of CMI Leaflets to those of Package Inserts. The experiment will use the Keystone Criteria (see Table 1) as standards for the overall quality of the leaflets. Each of the Keystone Criterion can be evaluated objectively with an automated system, with the exception of criterion #7, "Information must be scientifically accurate, unbiased, and up to date." In order to address that criterion, a domain expert would be required to determine whether the leaflet complies; this criterion is not included in the study.

Simple word comparisons or pattern matching are not sufficient for finding intersections between two documents, thus a text mining approach is needed. The text mining tools used must be nimble enough to recognize matches between documents written in very different styles. Package Inserts, as they are targeted at a professional audience, are likely to use different vocabulary than the CMI Leaflets, which are designed to be read by consumers. Several other classic NLP problems exist in the text as well.

One problem that is a common obstacle in text mining is dealing with synonymy. There are multiple ways to represent the same concepts in the English language. Simple pattern matching can be useful in conjunction with stemming. For example, the words, "testing", "tests", "tested" and "test" all have the same stem, "test", and are essentially synonymous. A stem is a root word from which other variations of the word are derived. It is then possible to match words from one document to the next by using the stemmed

word for pattern matching, and return a match regardless of the number or tense of the words.

Synonymy can go beyond different words meaning the same concept, to include similar concepts. For example, the terms “hypertension”, and “high blood pressure” are synonymous. However, a simple pattern match between these two words would erroneously produce a negative result.

Cimino refers to the “atomic approach” as a possible way to resolve synonymy in vocabulary. Word atoms are single words which when put together can form word molecules. Cimino uses the examples of the word molecules “White Conjunctiva” and “Wolff-Parkinson-White Syndrome” to illustrate this concept. The atom, “White”, can refer to either the color white, or to the name “White.” These atoms must be put in a molecular context in which the terms actually name a concept, not just exist as words which potentially have multiple meanings (Cimino, 1998).

Another problem is the comparison process in which terms from one document are to be matched to another document that is similar, but likely structured differently. This experiment will avoid the problems of lexical-level comparison by mapping words to CUIs, thus transforming the task into concept-level comparison. The problems of comparing differing sentence and paragraph structures in this experiment are avoided by treating each document as several bags of concepts in the form of CUIs. Each document is mapped to equivalent sections and each section is treated as a bag of concepts for comparison.

PI Heading	**Equivalent (First Databank) CMI Leaflet Heading**
Description	n/a
Microbiology and Clinical Pharmacology	General Information
Indications and Usage	Uses
Warnings	Warnings
Precautions	Precautions
Adverse Reactions	Side Effects
Overdosage	Overdose
Dosage and Administration	How to Use
How Supplied	n/a

Table 3: Package Insert headings with corresponding CMI Leaflet headings

As shown in Table 3, the overall structure of Package Inserts and CMI Leaflets produced by First Databank is fundamentally similar. The differences between the two documents are mainly noted in the “Description” and “How Supplied” sections. The

"Description" heading describes the drug at the chemical level, including chemical and structural formulas, and inert ingredients. The "How Supplied" section lists all forms of the medicine, such as: capsule, tablet, or liquid. These two sections are useful for health professionals, but not necessarily relevant to consumers, which is why they do not map to CMI Leaflet sections.

The "Microbiology and Clinical Pharmacology" section offers details about what biological mechanisms the drug uses, and also shows details of their clinical studies. While most of the information in this section is not particularly useful to consumers, part of this information is used in the "General Information" section of the CMI Leaflet.

To accomplish an inter-document comparison where the various documents are expected to use different vocabularies, a content analysis will be conducted using a text mining tool, MetaMap 2009 v2, which uses natural language processing and computational linguistic techniques. MetaMap is a Unified Medical Language System (UMLS) tool which is published by the National Institute of Health and the National Library of Medicine (Aronson, 2001). While it is used for information retreival and data mining, it is also used as a Medical Text Indexer, which automatically indexes biomedical literature at the National Library of Medicine. The UMLS contains a semantic network of terms in the metathesaurus. The metathesaurus covers the medical domain, including an extensive inventory of chemistry, medicine, pharmacology and biological terminologies.

MetaMap is a commonly used tool for Information Extraction (IE) for documents within the medical domain. Hsieh, Hardardottir, and Brennan (2004) were able to extract the meanings of email sent from patients to nurses using MetaMap to extract concepts.

The experiment showed MetaMap correctly captured the concepts in email approximately 53% of the time.

Erdal, Ding, Osborn, et al. (2007), used Metamap to create a prototype system to extract diagnosis information from free-form medical text and transform it into the form of an ICD-9 code. ICD-9 is a diagnosis code system which is used by medical facilities for billing. The ability to automatically code medical text for medical record coding specialists allows for a measure of quality control, as well as expediting coding and billing.

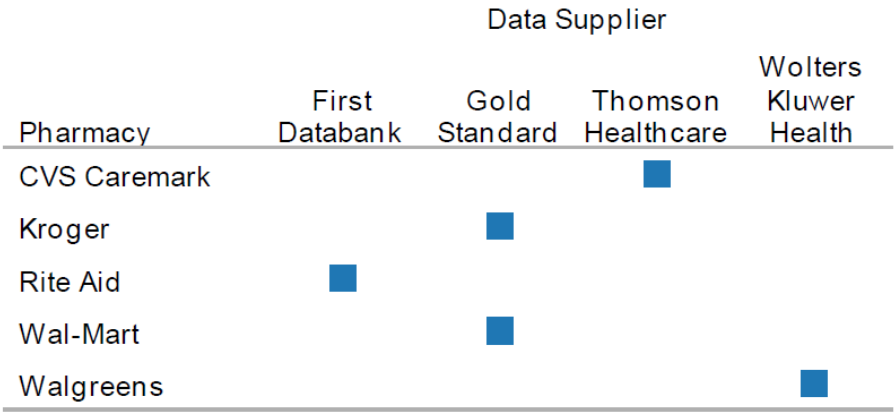
Pratt and Yetisgen-Yildiz (2003) showed that MetaMap was not only a viable tool for identifying concepts within unstructured text, but also could perform near the ability of a human. Their results suggest that MetaMap performed very well in the task of mapping common biomedical terms from free-form text. Its limitations were found to be concepts which were absent from the UMLS Metathesaurus, which drives MetaMap.

Chapman, Fiszman, Dowling, et al. (2004) used MetaMap to identify up to 71 clinical conditions from medical records which may potentially indicate lower respiratory syndrome, a condition which has public health implications. By using the CUI encoding, the experimenters were able to identify symptoms that were stated differently by different patients and that were coded differently by different doctors, in order to recognize when a patient could potentially have the targeted condition. The limitation of MetaMap in this study was found to be the resolution of abbreviations such as “pO2” instead of “percent oxygen”, for example.

MATERIALS

There are two distinct sets of data for this experiment: the Package Inserts and the CMI Leaflets. The Package Inserts were collected from the "Drugs@FDA" web site, which is an official repository of FDA-approved package inserts for drugs approved after 1998. Package Inserts are available on the Drugs@FDA web site in the form of PDF documents.

CMI Leaflets are not as closely regulated as Package Inserts; they are not hosted by any of the FDA's web sites. Several commercial information sources exist for CMI Leaflets. Which CMI Leaflet the consumer will encounter largely depends on the pharmacy they go to fill their prescription. A list of top grossing pharmacies was found at an online chain drug store industry news resource (Chain Drug Review, 2009). The top five pharmacies on this list in the United States as of 2009 were Walgreens, CVS



Caremark, Wal-Mart, Rite Aid, and Kroger.

Each of the top five pharmacies has online access to the CMI Leaflets they print for their customers. The web sites of each of these five pharmacies was visited, and the

Figure 2: Pharmacies and their leaflet data sources

source of the drug information provided to customers was identified (Fig. 2). The data providers for the CMI Leaflets were identified as: Wolters Kluwer Health, Thomson Healthcare, Gold Standard, and First Databank. Of these providers, First Databank, a subsidiary of The Hearst Corporation, is the largest provider of health information world-wide. In addition, First Databank is used as a drug summary resource on popular online health information web sites, such as WebMD and Medscape (WebMD, 2010) (Medscape, 2010). First Databank leaflets were chosen for use as the representative CMI Leaflets not only for their prevalence in the marketplace, but also because of their consistency. Every First Databank CMI Leaflet contains the sections listed in Table 4, which were easily mapped to Keystone Criteria.

Heading	**Keystone Criteria**
COMMON BRAND NAME(s)	#1: drug names and indications for use
USES	#1: drug names and indications for use
HOW TO USE THIS MEDICATION	#3: specific directions about how to use, monitor and get the most benefit
SIDE EFFECTS	#5: symptoms of serious or adverse frequent reactions and what to do
PRECAUTIONS	#4: specific precautions and how to avoid harm while using it
DRUG INTERACTIONS	#4: specific precautions and how to avoid harm while using it
OVERDOSE	#5: symptoms of serious or adverse frequent reactions and what to do
NOTES	#6: general information and encouragement to ask questions
MISSED DOSE	#3: specific directions about how to use, monitor and get the most benefit
STORAGE	#6: general information and encouragement to ask questions

Table 4: First Databank CMI Leaflet headings ordered by where they appear in the document

Two of the Keystone Criteria, #7 and #8, are not shown in Table 4. Criterion #7, "…scientifically accurate, unbiased, and up-to-date" did not map to any heading, and is not evaluated in this study. It cannot be evaluated automatically with the methods used in this experiment; a human expert would be required to evaluate what is accurate, unbiased and up-to-date. While Criterion #8, "…readily comprehensible and legible" did not map to a heading either, it will be evaluated on the documents as a whole, using the Flesch-Kincaid Grade Level metric.

PREPROCESSING

For the purpose of this study, 35 Package Inserts were collected. These inserts corresponded to the 35 most common prescription drugs filled in the U.S., based on overall quantity (Lamb, 2009). The PI data for this experiment was collected from the Drugs@FDA web site, and CMI Leaflets from revco.com, which exclusively uses First Databank as the leaflet provider. The quantity of drugs to be examined, 35, was determined as it is a number much greater than similar expert-evaluated studies which included five to six drugs, but a small enough number that it could be processed in a reasonable amount of time. Since both the CMI Leaflets and Package Inserts were being examined, a maximum of 70 (35 leaflets + 35 inserts) documents would have potentially required processing. However, generic drugs produced by multiple manufacturers had overlapping CMI leaflets. Because these drugs have the same drug name but are manufactured separately, there were only 66 documents (31 leaflets + 35 inserts) processed in total.

The documents were downloaded in PDF format and reduced to ASCII text by using “pdf2txt” software (http://www.pdf2txt.com). Charts and figures were removed from the corpus, as they could not properly be interpreted by MetaMap. The documents were also filtered and stripped of Unicode characters. MetaMap does not support non-ASCII characters, which excludes Unicode. These modifications to the data were completed using simple UNIX text processing tools such as awk, grep, sed, and cut. The text was then reformatted for compatibility with MetaMap (see Figure 3). Each document was broken into six sections to correspond with Keystone Criterion 1-6. The documents were then re-assembled into “MEDLINE” format (see Fig. 3), which is used by MetaMap for batch processing of data. This formatting consisted of adding a 9-digit Unique Identifier ("UI"), a Title (“TI”), and an Abstract section labeled (“AB”), where the text of the section was located. The UI was encoded based on the document type (1=PI,2=CMI), source (0=PI Manufacturer, 1=First Databank), drug (1-35), and section number (1-6) that corresponded to matching Keystone Criterion (see Table 4).

UI - 210200004
TI – FUROSEMIDE – ORAL FDB pt4
AB – DRUG INTERACTIONS:Your doctor or pharmacist may already be aware of any possible drug interactions and may be monitoring you for them. Do not start, stop, or change the dosage…

Figure 3: Sample text changed to MetaMap format for processing

METAMAP COMPARISON

MetaMap was used to transform all 35 Package Inserts and 30 CMI Leaflets to UMLS CUIs. A training set of five randomly-selected drugs from the corpus was used to determine which options to use with MetaMap. The options selected to pass to MetaMap for processing include removing stop words and stop phrases, such as “and”,

“the”, “by”, and other common words which occur often but do not have significance by themselves. MetaMap scores each of its matches based on the confidence of the match on a scale from 1 to 1000, with 1000 being the highest confidence. An option was given to MetaMap to limit matches to those rating to a score of at least 600 out of 1000 points in order to eliminate poor matches. The output from MetaMap was then uploaded into a database for analysis (see Fig. 4).

Drug Name	Manufacturer
Advair Diskus	GSK
Crestor	AstraZeneca
Cymbalta	Eli Lilly
Diovan	Novartis
Effexor XR	Wyeth
Lexapro	Forest Laboratories
Lipitor	Pfizer
Lisinopril	LEK Pharmaceuticals
Nexium	AstraZeneca
Plavix	Bristol-Myers Squibb
Prevacid	Takeda
Proair	TEVA
Seroquel	AstraZeneca
Simvastatin	Dr Reddys Laboratories
Singulair	Merck
Synthroid	Abbott
Vytorin	Merck/Schering-Plough
amlodipine besylate	Mylan
amoxicillin	TEVA
azithromycin	Greenstone
azithromycin	TEVA
cephalexin	Mikart
furosemide	Mylan
hydrochlorothiazide	TEVA
hydrocodone bitartrate and acetaminophen	Mallinkrodt (Coviden)
hydrocodone bitartrate and acetaminophen	Watson
levothyroxine sodium	Lannett Company
levothyroxine sodium	Mylan
metformin hydrochloride	TEVA
metoprolol tartrate	Mylan
metroprolol succinate	Ethex
oxycodone and acetaminophen	Mikart
sertraline hydrochloride	Greenstone
simvastatin	TEVA
warfarin sodium	TEVA

Table 5: Drugs and manufacturers included for analysis

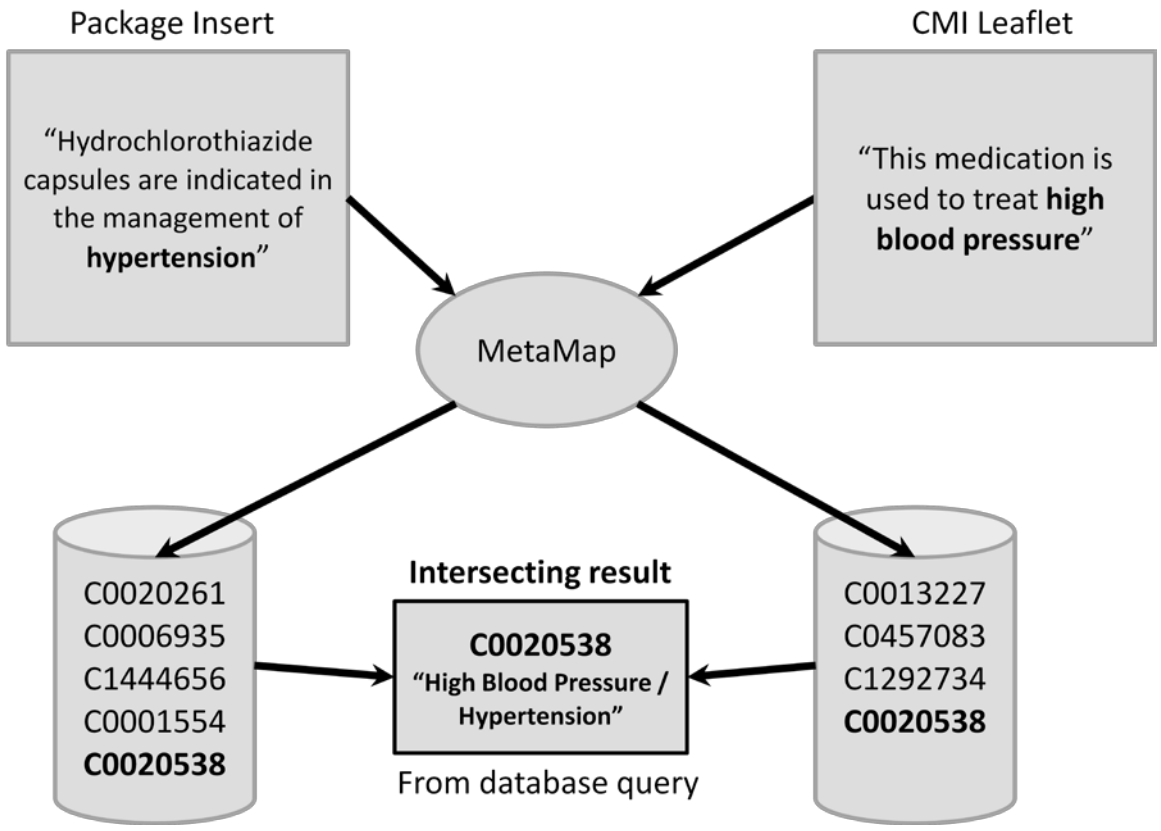


Figure 4: MetaMap analysis and bag-of-concepts comparison.

Each concept in the UMLS is represented by a Concept Unique Identifier (CUI). Each concept is also classified as one of 132 semantic types represented in the metathesaurus. By limiting results of MetaMap to relevant semantic types, performance can potentially be enhanced by eliminating some of the possibilities of multiple interpretations of phrases. For example, the word, "ventilation" can mean two things: a human physiologic function, or environmental air flow. By excluding the semantic type "environmental effect of humans," only "respiration" is considered as a candidate term. Other irrelevant semantic types removed from consideration serve to increase the accuracy of the MetaMap results. Using the training set, 32 semantic types were

identified for exclusion in the data options passed to MetaMap, such as: algae, amphibians, birds, fish, invertebrates, plants, etc. For example, concepts such as "amphibian" were unlikely to be used in either Package Inserts or CMI Leaflets. Table 6 gives the list of excluded types.

Alga	Geographic Area	Machine Activity	Occupational Activity	Physical Object	Reptile
Amphibian	Government or Regulatory Activity	Mammal	Organism	Plant	Research Activity
Animal	Group	Manufactured Object	Organism Attribute	Population Group	Research Device
Bird	Intellectual Product	Molecular Sequence	Organism Function	Professional Society	Self-help or Relief Organization
Eicosanoid	Invertebrate	Natural Phenomenon or Process	Organo-phosphorous Compound	Professional or Occupational Group	Temporal Concept
Fish	Language	Occupation or Discipline	Patient or Disabled Group	Regulation or Law	Vertebrate

Table 6: List of semantic types excluded by MetaMap

The analysis of the data output from MetaMap consisted of a bag-of-concepts analysis. For each of the Keystone Criteria 1-6, concepts extracted from the CMI Leaflets were compared to those extracted to the corresponding Package Inserts.

MEASURING PERFORMANCE

Though the system used in this experiment is not an information retrieval system per se, the concepts of precision and recall can be used to measure performance. For this study, the Package Insert was considered the gold standard, essentially containing all relevant CUIs, as the CMI leaflet is a subset based on the information contained in the

Package Insert. The system measures the recall of the CMI Leaflets, using the Package Insert as the gold standard. Precision is defined as all CUIs created for CMI Leaflets also found in Package Inserts.

$$precision = \frac{relevant\ CUIs}{returned\ CUIs}$$

$$recall = \frac{retrieved\ CUIs}{returned\ CUIs}$$

Precision is not measured for this study, since the CMI Leaflet is a summary of the Package Insert, and only the intersecting CUIs per Keystone Criteria are being counted. Precision will always be perfect (100%) in this case. As the CMI Leaflet is a subset of information based on the PI, it cannot contain more information than the original data, the Package Insert. Recall is defined as all CUIs generated from CMI Leaflets divided by the total CUIs generated from Package Inserts. Recall is expected to be quite low. This is because the Package Insert is written for readers with extensive medical and pharmacological knowledge, and contains terms which should be excluded completely from the summarized CMI Leaflet.

MEASURING READABILITY

Another dimension to consider for analysis is readability. This corresponds to Keystone Criterion #8, "Be readily comprehensible and legible." To analyze this, the Flesch-Kincaid Grade Level was used. The Flesch-Kincaid Grade Level metric is a representation of the readability of the document equivalent to the mean number of school years, or grades, needed to properly comprehend its content. The grade level

produced by the metric is based on U.S. grade levels (Kincaid, Fishburne, Rogers, 1975). The Flesch-Kincaid Grade Level metric is calculated using the following formula:

$$Grade\ Level = \left(0.39 \times \frac{total\ words}{total\ sentences}\right) + \left(11.8 \times \frac{total\ syllables}{total\ words}\right) - 15.59$$

To measure the Flesch-Kincaid score on the corpus, each document was preprocessed, with numbers and charts removed, as these would otherwise distort the syllable count. After preprocessing, the words and syllables were counted. The results were then entered into a database, where the grade level score formula was calculated for each document as a whole.

As it is estimated that 50% of adult Americans read at or below the 8th grade level, a Flesch-Kincaid Grade Level score of 8.5 or lower should be considered readable by adults. (U.S. Dept of Education, 2010) It would thus be desirable for CMI Leaflets to meet that readability standard. Package Inserts are written to comply with FDA rules and require FDA approval. They are required to be thorough and contain information used for the approval process, including study information, and other pharmacology and medical terms which are not in the general public's vocabulary. Therefore, a much higher grade level readability score is anticipated for the Package Inserts.

RESULTS

The pre-processed corpus used in this study consisted of a total of 944,153 words. Metamap generated 91,746 CUI instances from the corpus. MetaMap CUI production showed Package Inserts producing significantly more CUI than CMI Leaflets, as expected (see Table 7).

Table 8 shows recall for each drug broken out by criterion. The overall maximum recall was 29.9%, and minimum was 0.6%, (see Table 8). Figure 7 shows a visualization of mean recall for each criterion. Patterns of particular interest can be found in Keystone Criteria 1, 2, an d 4, and will be discussed later.

	Mean number of CUI per document	**Minimum number of CUI per document**	**Maximum number of CUI per document**
CMI Leaflet	188	70	783
PI	496	130	7051

Table 7: CUI production per document type

		Keystone Criteron					
Drug	Manufacturer	1	2	3	4	5	6
Advair Diskus	GSK	4.00	3.45	19.62	14.05	11.88	20.79
amlodipine besylate	Mylan	4.26	2.65	4.57	10.29	7.95	7.19
amoxicillin	TEVA	25.00	2.67	3.14	14.45	16.67	13.06
azithromycin	Greenstone	4.55	0.59	10.64	19.94	4.60	11.12
	TEVA	11.11	8.33	15.29	19.22	4.02	12.36
cephalexin	Mikart	7.37	3.11	17.51	12.71	9.53	7.29
Crestor	AstraZeneca	12.50	2.70	8.95	9.97	1.52	7.68
Cymbalta	Eli Lilly	3.46	4.73	16.14	8.24	13.51	9.31
Diovan	Novartis	11.22	2.88	14.15	10.85	11.94	11.34
Effexor XR	Wyeth	12.50	2.33	3.88	9.62	6.90	3.03
furosemide	Mylan	2.04	3.51	21.21	15.49	11.36	18.80
hydrochlorothiazide	TEVA	12.50	2.80	5.93	13.66	11.11	5.26
hydrocodone bitartrate and acetaminophen	Mallinkrodt (Coviden)	12.50	1.85	1.16	13.55	7.27	11.76
	Watson	14.29	2.17	11.83	10.26	0.83	29.91
levothyroxine sodium	Lannett Company	12.50	1.45	10.34	21.29	1.51	0.93
	Mylan	12.50	2.56	16.67	13.51	1.17	0.75
Lexapro	Forest Laboratories	4.08	0.89	10.09	11.58	8.72	0.78
Lipitor	Pfizer	6.09	3.39	16.62	12.46	8.73	7.29
Lisinopril	LEK Pharmaceuticals	9.41	1.01	7.11	16.10	5.61	3.19
metformin hydrochloride	TEVA	4.95	6.23	18.85	10.64	12.40	6.13
metoprolol succinate	Ethex	6.46	4.47	17.68	11.85	10.65	6.44
metoprolol tartrate	Mylan	5.88	1.37	8.59	20.23	2.63	1.20
Nexium	AstraZeneca	6.12	0.89	12.84	13.89	4.74	7.35
oxycodone and acetaminophen	Mikart	11.11	3.39	2.08	11.17	4.07	6.57
Plavix	Bristol-Myers Squibb	20.00	2.70	10.03	11.24	10.11	2.70
Prevacid	Takeda	4.84	6.89	17.01	10.55	14.25	8.12
Proair	TEVA	9.67	9.96	33.43	19.53	25.83	17.16
Seroquel	AstraZeneca	3.97	6.86	16.99	9.69	13.15	9.04
setraline hydrochloride	Greenstone	3.86	5.48	16.30	9.29	14.80	9.94
simvastatin	Dr Reddys Laboratories	3.64	5.85	16.18	8.40	13.70	9.58
	TEVA	10.00	2.27	6.75	8.66	8.12	8.42
Singulair	Merck	12.50	2.13	25.51	20.10	1.28	19.35
Synthroid	Abbott	27.60	10.87	9.31	19.54	9.12	14.58
vytorin	Merck/Schering-Plough	4.43	6.35	18.35	10.88	12.81	6.97
warfarin sodium	TEVA	3.42	0.67	6.74	8.95	5.43	14.47

Table 8: CUI recall for Keystone Criterion 1-6 for each drug

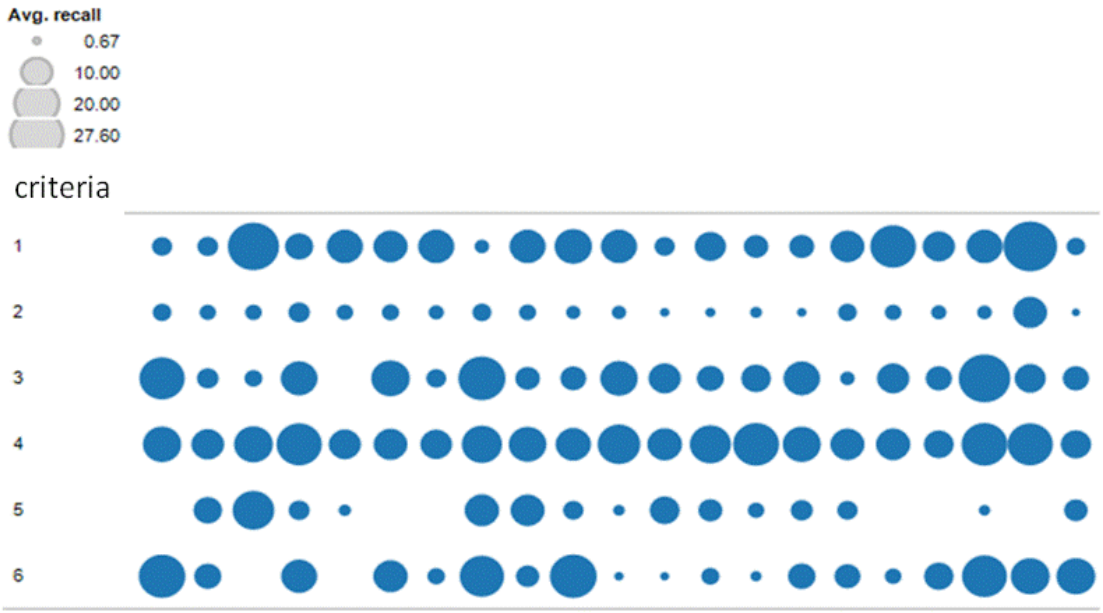


Figure 7: Summary of Recall of CUI by Keystone Criteria

Drug	Manufacturer	Mean	Min	Max
Advair Diskus	GSK	12.30	3.45	20.79
amlodipine besylate	Mylan	6.15	2.65	10.29
amoxicillin	TEVA	12.50	2.67	25.00
azithromycin	Greenstone	8.57	0.59	19.94
	TEVA	11.72	4.02	19.22
cephalexin	Mikart	9.59	3.11	17.51
Crestor	AstraZeneca	7.22	1.52	12.50
Cymbalta	Eli Lilly	9.23	3.46	16.14
Diovan	Novartis	10.40	2.88	14.15
Effexor XR	Wyeth	6.38	2.33	12.50
furosemide	Mylan	12.07	2.04	21.21
hydrochlorothiazide	TEVA	8.55	2.80	13.66
hydrocodone bitartrate and acetaminophen	Mallinkrodt (Covidien)	8.02	1.16	13.55
	Watson	11.55	0.83	29.91
levothyroxine sodium	Lannett Company	8.00	0.93	21.29
	Mylan	7.86	0.75	16.67
Lexapro	Forest Laboratories	6.02	0.78	11.58
Lipitor	Pfizer	9.10	3.39	16.62
Lisinopril	LEK Pharmaceuticals	7.07	1.01	16.10
metformin hydrochloride	TEVA	9.87	4.95	18.85
metoprolol succinate	Ethex	9.59	4.47	17.68
metoprolol tartrate	Mylan	6.65	1.20	20.23
Nexium	AstraZeneca	7.64	0.89	13.89
oxycodone and acetaminophen	Mikart	6.40	2.08	11.17
Plavix	Bristol-Myers Squibb	9.46	2.70	20.00
Prevacid	Takeda	10.28	4.84	17.01
Proair	TEVA	9.63	3.53	18.34
Seroquel	AstraZeneca	9.95	3.97	16.99
setraline hydrochloride	Greenstone	9.95	3.86	16.30
simvastatin	Dr Reddys Laboratories	9.56	3.64	16.18
	TEVA	7.37	2.27	10.00
Singulair	Merck	13.48	1.28	25.51
Synthroid	Abbott	15.17	9.12	27.60
vytorin	Merck/Schering-Plough	9.96	4.43	18.35
warfarin sodium	TEVA	6.61	0.67	14.47

Table 9: Mean, Minimum, and Maximum Recall for each drug

Keystone Criteron	Mean	Min	Max
1	8.90	2.04	27.60
2	3.60	0.59	10.87
3	12.54	1.16	25.51
4	12.83	8.24	21.29
5	8.55	0.83	16.67
6	9.16	0.75	29.91

Table 10: Mean, Minimum, and Maximum Recall for each criterion

Figure 8 is a visualization of reading grade levels for the Package Inserts and CMI Leaflets in this study. Differences in reading levels are shown between the two document types, as evidenced by two distinct columns of reading levels representing the CMI Leaflet at lower reading levels, and PI at higher reading levels. The average grade reading levels were 8.75 for CMI Leaflets and 14.45 for Package Inserts.

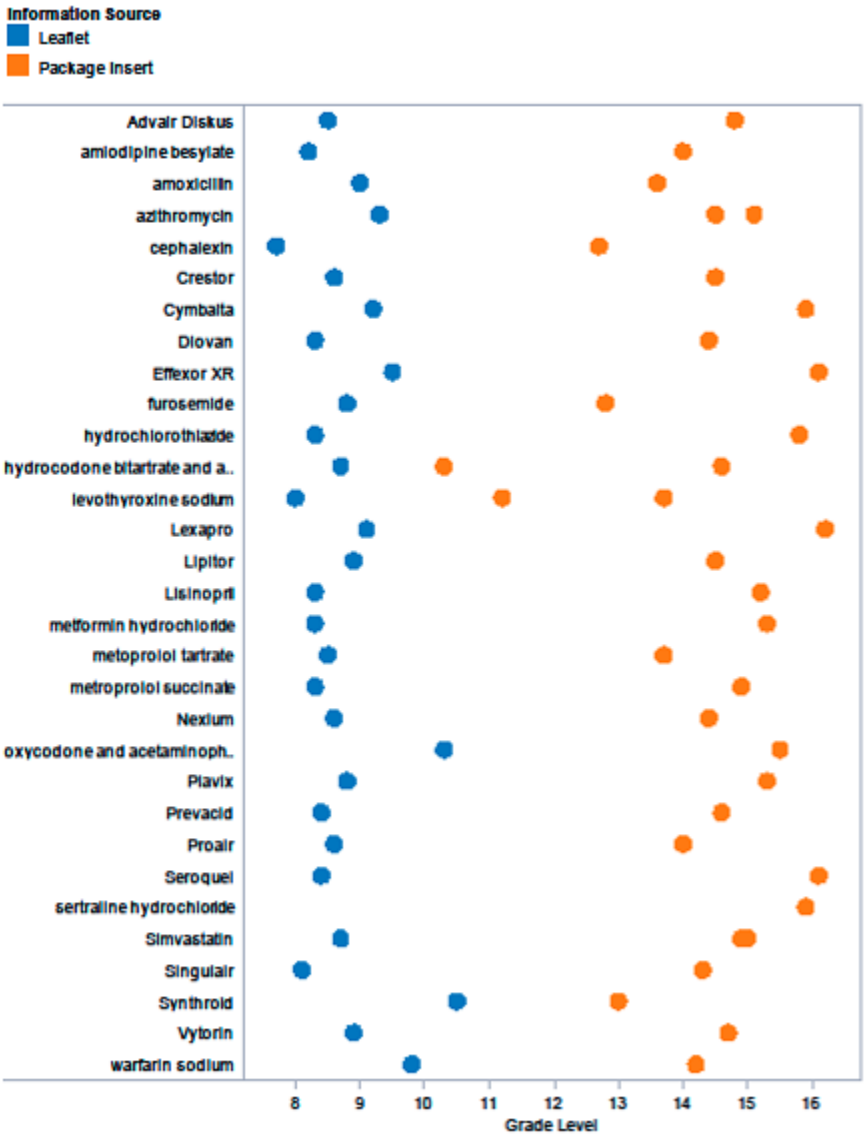


Figure 8: Flesch-Kincaid reading grade level scores for CMI Leaflet and PI

DISCUSSION

Criteron 1 is “drug name and indications for use.” In many cases, the PI and CMI Leaflet recall levels differed among drugs as illustrated in Figure 7. CMI Leaflets associated with drugs with a narrower scope of use acheived a higher recall percentage than average. One example is Synthroid, a synthetic thyroid hormone replacement medication which only has one purpose. It had a relatively high recall (mean: 15.17%, min: 9.12%, max: 27.6%), indicating that this section of the leaflet contained most of the CUIs used in the PI. Amoxicillin, an antibiotic to treat infections, performed similarly. Furosemide, a drug with a broader scope of use as a diuretic used for treating a variety of conditions such as liver disease, kidney disease, heart disease, ranked lowest, at 2.0% recall. The CMI Leaflet mentions *some* of the general uses of the drug, but the Package Insert lists *all* approved uses, which is a much larger list.

Criterion 2 is “contraindications and what to do if applicable.” The CMI Leaflets as a whole had very little information about contraindications. The few that did have particularly dangerous contraindications ranked higher in recall for this criterion. Drugs with special warnings of contraindications were likely to have a higher recall percentage. One example was Synthroid, which listed many over the counter (OTC) medications that could interfere with its absorption, or would adversely interact with it, found in the ”Drug Interactions” section of the CMI Leaflet.

Criterion 4 is “specific precautions and how to avoid harm while using it.” The results shown in Figure 7 show a relatively flat recall across all the CMI Leaflets compared to the other criteria. The reason for this is the prevalence of standardized

wording in the CMI Leaflet to address general precautions when using any medication. Individual differences in medications were the cause of the minor differences between drug CMI Leaflets, interjecting extra information within the standardized block of text.

Another issue which is revealed in the pattern in Figure 7, criterion 4 appears to have a higher recall due to standardized wording used by the leaflet information company for this section. The following sample can be found in each drug's "Precautions" section in the CMI Leaflet:

> "Before taking **[DRUG]**, tell your doctor or pharmacist if you are allergic to it; or if you have any other allergies. This product may contain inactive ingredients, which can cause allergic reactions or other problems… Talk to your pharmacist for more details. This medication should not be used if you have certain medical conditions. Before using this medication, tell your doctor or pharmacist your medical history… Before having surgery, tell your doctor or dentist that you are taking this medication. Your doctor may instruct you to stop **[DRUG]** prior to surgery… Discuss the risks and benefits with your doctor. It is not known whether this drug passes into breast milk. Breast-feeding is not recommended while using this drug. Consult your doctor before breast-feeding..."

Criterion 5 is "symptoms of serious or frequent adverse reactions and what to do." The recall results for this are quite variable. Most drugs listed in the top 35 filled prescription drugs in the U.S. do not have common frequent adverse reactions. The drugs that do have common adverse reactions had a high recall, while others with rare adverse reactions had a low recall. This is because the FDA mandates that every adverse reaction documented with this drug be present in the Package Insert, but not in the CMI Leaflet.

Criterion 6 is "general information and encouragement to ask questions." This criterion also showed a large variation in recall. While there is no section in the PI for "encouragement to ask questions", general information is found in the Clinical Pharmacology section. As most of the information found in this section of the PI is not

particularly useful for consumers, recall is expected to be quite low. However, in Package Inserts with less clinical data presented, CMI Leaflets are able to intersect the main concepts with a higher recall percentage.

Criterion 8, “comprehensibility and legibility”, was measured by using the Flesch-Kincaid grade level score. As shown in Figure 8, reading levels are vastly different between the Leaflet and Package Insert documents. This result is consistent with expectations, as the PI and CMI Leaflets have different intended audiences.

In this experiment, the Leaflets were drawn from a single source, First Databank. This may explain the relative consistency of the grade level scores, 73% of which fall between 8th and 9th grade reading levels. Leaflets falling out of this range typically tracked upward in grade level to a maximum of grade level 10.5. The Leaflets with the higher grade level score also correlated to medications which scored lower in CUI intersections for Keystone Criterion 1-6.

Package Inserts were rated with a maximum grade level score of 16.5, which would, in theory, challenge graduate students' reading comprehension. The range of grade levels, as shown in Figure 8, is slightly more diverse than what is found in CMI Leaflets, but also follows the same trend of difficulty based on the drug. Drugs which have longer, more complicated sets of instructions, warnings, and other facts seem to reflect higher grade level scores in both the Package Insert and the CMI Leaflet, as exemplified by Synthroid, the synthetic thyroid hormone, and Lexapro, an antidepressant.

Generic drugs are produced by different manufacturers under the same drug names. Since each manufacturer is responsible for writing their own PI, the information

could potentially be different between manufacturers. Surprisingly, there was a great deal of variation between the PI documentation between manufacturers of the same generic drug, particularly in reading level, as shown in Figure 8.

The readability goal of the 8th grade level as a target for the Leaflet data provider in the study was not met exactly, but it was close. Forty-three percent of the CMI Leaflets for the top 35 drugs were at or below the 8th grade reading level. A modest effort to simplify the text would likely open up this information to more of the population.

SUMMARY AND CONCLUSIONS

Through examining recall of CUI terms in Package Inserts in from CMI Leaflets, it was found that there was a fairly low recall percentage between the two documents. However, this is to be expected, as the CMI Leaflet is intended to be brief, factual, and usable, whereas the Package Insert is designed to be extremely thorough.

The reading levels shown by the Flesch-Kincaid grade level scores are consistent. The rated grade level of the CMI Leaflets averaged in the 8th to 9th grade range, while the PI were in the 14th-15th grade range. This result points to the readability of the CMI Leaflets, being easily readable by much of the U.S. population.

Of the results obtained by this study, possibly the most telling is that Criterion 4, precautions and how to avoid harm using the drug, was virtually the same for many CMI leaflets (see Fig. 7). Specific precautions were generally not given, rather a more generic statement of what to do if a reaction is noticed was given. This supports the conclusion of Raynor, Svarstad, Knapp, et al. (2007), that U.S. CMI leaflets are weak in that area.

The Package Insert is public information which anyone can obtain, and is full of data which could be useful for patients. The drug interactions omitted from CMI Leaflets are generally unusual and not life-threatening. However, the danger in writing summaries where an individual's well-being is potentially at stake is the possibility of becoming complacent about omitting information about rare effects or consequences of the drug.

This study has shown that text mining tools such as MetaMap may be able to evaluate drug information documents such as Package Inserts and CMI Leaflets without the expense of an expert evaluator. However, there is future work to be done.

One direction future research can go in is to compare results of an automated evaluation system those of a human expert evaluator. This study did not address how an automated system compares to human evaluators, but this is an important issue to address before suggesting that text mining technology replace human evaluators for this task.

Future research could also better examine the fundamental differences in content between PI and CMI Leaflets. While this experiment shows recall and grade level metrics, more work can be done on what types of data are consistently shared between PI and CMI, and what data are missing. For example, it may prove useful to identify whether or not specific information such as the effect of a drug during pregnancy or with other conditions reaches the patient through the CMI Leaflet.

Lastly, the scale of this study was small, only evaluating the top 35 filled prescriptions in the U.S., and exclusively using First Databank as the information source for CMI Leaflets. Ideally, a larger sample of drugs should be used in future studies, as well as a larger sample of CMI Leaflet providers, given the lower cost of automatic

evaluation instead of human expert evaluators. More work in automatic evaluation of drug information documents on a larger scale is warranted.

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APPENDIX

Sample MetaMap Output (Package Insert- Warfarin sodium)

Processing 100003501.ti.1: WARFARIN SODIUM warfarin sodium tablet pt1

Phrase: "WARFARIN SODIUM warfarin sodium tablet pt1"
Meta Mapping (774):
  660 C0376218:Warfarin Sodium [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
  632 C0039225:Tablet (Tablet Dosage Form) [Biomedical or Dental Material]
Meta Mapping (774):
  660 C0376218:Warfarin Sodium [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
  632 C1705223:Tablet (Tablet Dosing Unit) [Quantitative Concept]
Processing 100003501.ab.1: INDICATIONS AND USAGE: Warfarin sodium tablets are indicated for the prophylaxis andor treatment of venous thrombosis and its extension and pulmonary embolism.

Phrase: "INDICATIONS"
Meta Mapping (1000):
  1000 C0392360:Indications (Indication of (contextual qualifier)) [Idea or Concept]

Phrase: "AND"
Phrase: "USAGE"
Meta Mapping (1000):
  1000 C0457083:Usage [Functional Concept]

Phrase: ":"

Phrase: "Warfarin sodium tablets"
Meta Mapping (901):
  734 C0376218:Warfarin Sodium [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
  827 C0039225:Tablets (Tablet Dosage Form) [Biomedical or Dental Material]

Phrase: "are"

Phrase: "indicated"
Meta Mapping (1000):
  1000 C1444656:Indicated [Finding]

Phrase: "for the prophylaxis andor treatment"
Meta Mapping (877):
  877 C0199176:Prophylactic treatment [Therapeutic or Preventive Procedure]
Phrase: "of venous thrombosis"
Meta Mapping (1000):
  1000 C0042487:Venous Thrombosis [Pathologic Function]
Meta Mapping (1000):
  1000 C0517555:Venous thrombosis (Venous thrombosis after immobility) [Finding]

Phrase: "and"

Phrase: "its extension"
Meta Mapping (1000):
  1000 C0231448:Extension [Functional Concept]
Meta Mapping (1000):
  1000 C1880641:Extension (Telephone Extension Number) [Conceptual Entity]

Phrase: "and"

Phrase: "pulmonary embolism."
Meta Mapping (1000):
1000 C0034065:Pulmonary Embolism [Disease or Syndrome]
Processing 100003501.ab.2: Warfarin sodium tablets are indicated for the prophylaxis andor treatment of the thromboembolic complications associated with atrial fibrillation andor cardiac valve replacement.
Phrase: "Warfarin sodium tablets"
Meta Mapping (901):
734 C0376218:Warfarin Sodium [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
827 C0039225:Tablets (Tablet Dosage Form) [Biomedical or Dental Material]

Phrase: "are"

Phrase: "indicated"
Meta Mapping (1000):
1000 C1444656:Indicated [Finding]

Phrase: "for the prophylaxis andor treatment"
Meta Mapping (877):
877 C0199176:Prophylactic treatment [Therapeutic or Preventive Procedure]

Phrase: "of the thromboembolic complications"
Meta Mapping (888):
694 C0333214:Thromboembolic [Functional Concept]
861 C0009566:Complications (Complication) [Pathologic Function]
Meta Mapping (888):
694 C0333214:Thromboembolic [Functional Concept]
861 C1171258:complications (Complication Aspects) [Pathologic Function]
Phrase: "associated"
Meta Mapping (1000):
1000 C0332281:Associated (Associated with) [Qualitative Concept]

Phrase: "with atrial fibrillation andor cardiac valve replacement."
Meta Mapping (786):
660 C0004238:Atrial Fibrillation [Pathologic Function]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C1555302:Replacement (Act Code - Replacement) [Idea or Concept]
Meta Mapping (786):
660 C0004238:Atrial Fibrillation [Pathologic Function]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0559956:Replacement [Functional Concept]
Meta Mapping (786):
660 C0004238:Atrial Fibrillation [Pathologic Function]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0035139:Replacement (Surgical Replantation) [Therapeutic or Preventive Procedure]
Meta Mapping (786):
660 C1963067:Atrial fibrillation (Atrial Fibrillation Adverse Event) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C1555302:Replacement (Act Code - Replacement) [Idea or Concept]
Meta Mapping (786):
660 C1963067:Atrial fibrillation (Atrial Fibrillation Adverse Event) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0559956:Replacement [Functional Concept]
Meta Mapping (786):
660 C1963067:Atrial fibrillation (Atrial Fibrillation Adverse Event) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0035139:Replacement (Surgical Replantation) [Therapeutic or Preventive Procedure]
Meta Mapping (786):
660 C2108067:atrial fibrillation (continuous electrocardiogram atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C1555302:Replacement (Act Code - Replacement) [Idea or Concept]
Meta Mapping (786):

660 C2108067:atrial fibrillation (continuous electrocardiogram atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0559956:Replacement [Functional Concept]
Meta Mapping (786):
660 C2108067:atrial fibrillation (continuous electrocardiogram atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0035139:Replacement (Surgical Replantation) [Therapeutic or Preventive Procedure]
Meta Mapping (786):
660 C2041124:atrial fibrillation (electrocardiogram rhythm strip 3-lead atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C1555302:Replacement (Act Code - Replacement) [Idea or Concept]
Meta Mapping (786):
660 C2041124:atrial fibrillation (electrocardiogram rhythm strip 3-lead atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0559956:Replacement [Functional Concept]
Meta Mapping (786):
660 C2041124:atrial fibrillation (electrocardiogram rhythm strip 3-lead atrial fibrillation) [Finding]
660 C0018826:Cardiac valve (Heart Valves) [Body Part, Organ, or Organ Component]
799 C0035139:Replacement (Surgical Replantation) [Therapeutic or Preventive Procedure]
Processing 100003501.ab.3: Warfarin sodium tablets are indicated to reduce the risk of death recurrent myocardial infarction and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

Phrase: "Warfarin sodium tablets"
Meta Mapping (901):
734 C0376218:Warfarin Sodium [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
827 C0039225:Tablets (Tablet Dosage Form) [Biomedical or Dental Material]

…

Sample MetaMap Output (First Databank Leaflet- Warfarin sodium)

Processing 212600001.ti.1: WARFARIN - ORAL FDB pt1

Phrase: "WARFARIN - ORAL FDB pt1"
Meta Mapping (775):
645 C0043031:Warfarin [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
645 C0442027:Oral [Spatial Concept]
Processing 212600001.ab.1: COMMON BRAND NAME(S):Coumadin WARNING:Warfarin can cause very serious (possibly fatal) bleeding.

Phrase: "COMMON BRAND NAME"
Meta Mapping (623):
660 C0205214:Common (Common (qualifier value)) [Quantitative Concept]
660 C0645690:BrAnd (3-bromoacetoxyandrostan-17-one) [Pharmacologic Substance,Steroid]
Meta Mapping (623):
660 C1522138:Common (shared attribute) [Functional Concept]
660 C0645690:BrAnd (3-bromoacetoxyandrostan-17-one) [Pharmacologic Substance,Steroid]

Phrase: "(S):Coumadin WARNING"
Meta Mapping (660):
660 C0699129:Coumadin [Organic Chemical,Pharmacologic Substance]

Phrase: ":"

Phrase: "Warfarin"
Meta Mapping (1000):
1000 C0043031:Warfarin [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]

Phrase: "can"

Phrase: "cause"
Meta Mapping (1000):
  1000 C1524003:Cause (Science of Etiology) [Conceptual Entity]

Phrase: "very serious"
Meta Mapping (888):
  694 C0442824:Very [Qualitative Concept]
  861 C0205404:Serious [Qualitative Concept]

Phrase: "(possibly fatal"
Meta Mapping (888):
  694 C0332149:POSSIBLY (Possible) [Qualitative Concept]
  861 C1705232:FATAL (Death Related to Adverse Event) [Finding]
Meta Mapping (888):
  694 C0332149:POSSIBLY (Possible) [Qualitative Concept]
  861 C1302234:Fatal [Qualitative Concept]
Meta Mapping (888):
  694 C2362652:Possibly (Possible diagnosis) [Qualitative Concept]
  861 C1705232:FATAL (Death Related to Adverse Event) [Finding]
Meta Mapping (888):
  694 C2362652:Possibly (Possible diagnosis) [Qualitative Concept]
  861 C1302234:Fatal [Qualitative Concept]

Phrase: ")"

Phrase: "bleeding."
Meta Mapping (1000):
  1000 C0019080:Bleeding (Hemorrhage) [Finding]
Processing 212600001.ab.2: This is more likely to occur when you first start taking this medication and/or when you are taking too much warfarin.

Phrase: "This"

Phrase: "is"

Phrase: "more likely to"
Meta Mapping (827):
  827 C0332148:Likely (Probable diagnosis) [Qualitative Concept]

Phrase: "occur"
Meta Mapping (1000):
  1000 C1709305:Occur [Conceptual Entity]

Phrase: "when"

Phrase: "you first"
Meta Mapping (1000):
  1000 C0205435:First (First (number)) [Quantitative Concept]
Meta Mapping (1000):
  1000 C1279901:First (Firstly) [Qualitative Concept]

Phrase: "start"
Meta Mapping (966):
  966 C1272689:Started [Qualitative Concept]

Phrase: "taking"
Meta Mapping (966):
  966 C1883727:Taken [Conceptual Entity]

Phrase: "this medication"

Meta Mapping (1000):
  1000 C0013227:Medication, NOS (Pharmaceutical Preparations) [Pharmacologic Substance]

Phrase: "and/or"

Phrase: "when"

Phrase: "you"

Phrase: "are"
Phrase: "taking"
Meta Mapping (966):
  966 C1883727:Taken [Conceptual Entity]

Phrase: "too"

Phrase: "much warfarin."
Meta Mapping (1000):
  1000 C0043031:Warfarin [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
Processing 212600001.ab.3: To decrease your risk for bleeding, your doctor or other health care provider will monitor you closely and check your lab results (INR test) to make sure you are not taking too much warfarin.

Phrase: "To"

Phrase: "decrease"
Meta Mapping (1000):
  1000 C0547047:Decrease [Quantitative Concept]
Meta Mapping (1000):
  1000 C0392756:Decrease (Reduced) [Qualitative Concept]

Phrase: "your risk"
Meta Mapping (1000):
  1000 C0035647:Risk [Qualitative Concept]

Phrase: "for bleeding,"
Meta Mapping (1000):
  1000 C0019080:Bleeding (Hemorrhage) [Finding]

Phrase: "your doctor"
Meta Mapping (1000):
  1000 C2348314:Doctor (Doctor - Title) [Conceptual Entity]

Phrase: "or"

Phrase: "other health care provider"
Meta Mapping (851):
  612 C1955473:Others [Finding]
  694 C0086388:Health Care [Health Care Activity]
  812 C1555587:provider (Act Code - provider) [Idea or Concept]
Meta Mapping (851):
  612 C1955473:Others [Finding]
  694 C0086388:Health Care [Health Care Activity]
  812 C1441436:{Provider} [Health Care Activity]

Phrase: "will"

Phrase: "monitor"
Meta Mapping (1000):
  1000 C0181904:Monitor (Biomedical Monitors) [Medical Device]
Meta Mapping (1000):
  1000 C1704646:Monitor (Monitor Device Component) [Manufactured Object]

Meta Mapping (1000):
  1000 C0596972:Monitor (Monitoring Device) [Medical Device]

Phrase: "you closely"
Meta Mapping (928):
  928 C0587267:Close (Closed) [Functional Concept]
Meta Mapping (928):
  928 C1522666:Closest [Spatial Concept]

Phrase: "and"

Phrase: "check"
Meta Mapping (1000):
  1000 C1948051:Check (Checking) [Qualitative Concept]

Phrase: "your lab results"
Meta Mapping (870):
  661 C0237076:Labs (Laboratory Finding) [Laboratory or Test Result]
  861 C1274040:Results (result) [Functional Concept]

Phrase: "(INR test"
Meta Mapping (1000):
  1000 C0851084:INR test [Laboratory Procedure]

Phrase: ")"

Phrase: "to"

Phrase: "make"
Meta Mapping (1000):
  1000 C1881534:Make (Make - Instruction Imperative) [Functional Concept]

Phrase: "sure you"

Phrase: "are"

Phrase: "not"
Meta Mapping (1000):
  1000 C1518422:Not (Negation) [Functional Concept]

Phrase: "taking"
Meta Mapping (966):
  966 C1883727:Taken [Conceptual Entity]

Phrase: "too"

Phrase: "much warfarin."
Meta Mapping (1000):
  1000 C0043031:Warfarin [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
Processing 212600001.ab.4: Keep all medical and laboratory appointments.

Phrase: "Keep"
Phrase: "all medical"
Meta Mapping (1000):
  1000 C0205476:Medical [Functional Concept]

Phrase: "and"

Phrase: "laboratory appointments."
Meta Mapping (861):
  861 C0003629:Appointments [Idea or Concept]

Processing 212600001.ab.5: Tell your doctor immediately if you notice any signs of serious bleeding.

Phrase: "Tell"

Phrase: "your doctor immediately"
Meta Mapping (861):
  861 C2348314:Doctor (Doctor - Title) [Conceptual Entity]

Phrase: "if"

Phrase: "you"

Phrase: "notice"

Phrase: "any signs"
Meta Mapping (1000):
  1000 C0220912:signs (Aspects of signs) [Functional Concept]
Meta Mapping (1000):
  1000 C0220913:Signs (Manufactured sign) [Manufactured Object]
Meta Mapping (1000):
  1000 C0311392:SIGNS (Physical findings) [Finding]

Phrase: "of serious bleeding."
Meta Mapping (888):
  694 C0205404:Serious [Qualitative Concept]
  861 C0019080:Bleeding (Hemorrhage) [Finding]
Processing 212600001.ab.6: See also Side Effects section.

Phrase: "See"
Meta Mapping (966):
  966 C0205397:Seen [Qualitative Concept]
Meta Mapping (966):
  966 C0183089:SAW (saw (device)) [Medical Device]

Phrase: "also Side Effects"
Meta Mapping (901):
  901 C0879626:side effects (Adverse effects) [Pathologic Function]
Meta Mapping (901):
  901 C0001688:side effects (aspects of adverse effects) [Functional Concept]

Phrase: "section."
Meta Mapping (1000):
  1000 C1293097:Section, NOS (Division (procedure)) [Therapeutic or Preventive Procedure]
Meta Mapping (1000):
  1000 C0205155:Section (Sectional Distribution) [Spatial Concept]
Meta Mapping (1000):
  1000 C1552923:Section (Square Mile) [Quantitative Concept]
Meta Mapping (1000):
  1000 C1522472:Section (section sample) [Substance]
Processing 212600002.ti.1: WARFARIN - ORAL FDB pt2

Phrase: "WARFARIN - ORAL FDB pt2"
Meta Mapping (775):
  645 C0043031:Warfarin [Hazardous or Poisonous Substance,Organic Chemical,Pharmacologic Substance]
  645 C0442027:Oral [Spatial Concept]
Processing 212600002.ab.1: USES:This medication is used to treat blood clots (such as in deep vein thrombosis-DVT or pulmonary embolus-PE) and/or to prevent new clots from forming in your body.

Phrase: "USES"
Meta Mapping (966):
  966 C0457083:Use (Usage) [Functional Concept]

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Meta Mapping (966):
  966 C0042153:use (utilization qualifier) [Functional Concept]

Phrase: ":"

Phrase: "This medication"
Meta Mapping (1000):
  1000 C0013227:Medication, NOS (Pharmaceutical Preparations) [Pharmacologic Substance]

Phrase: "is"

Phrase: "used to"
Meta Mapping (827):
  827 C0457083:Use (Usage) [Functional Concept]
Meta Mapping (827):
  827 C1524063:Using (Use of) [Functional Concept]
Meta Mapping (827):
  827 C0042153:use (utilization qualifier) [Functional Concept]

Phrase: "treat"
Meta Mapping (1000):
  1000 C1522326:Treat (Treating) [Functional Concept]…
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